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# CD44 and hyaluronan help mesenchymal stem cells move to a neighborhood in need of regeneration

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**Prevention of normal interactions between CD44 cell-surface receptors on cultured mesenchymal stem cells and hyaluronic acid in the renal interstitial matrix has been described as reducing the ability of these cells *in vivo* to localize to regions with acute tubular injury. Understanding processes such as this might one day help us to target exogenous cells to assist renal regeneration.**

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Mesenchymal stem cells (MSCs), established as being important in maintaining the niche occupied by hematopoietic stem cells,[1] have been reported to be capable of much more. A spectrum of studies, more than can be cited in this Commentary, have suggested that exogenous bone marrow cells, purified hematopoietic stem cells, or cultured MSCs may infiltrate mouse tissues and in particular circumstances affect the course of renal damage. Results from acute renal injury models, using glycerol,[2] ischemia–reperfusion,[3] cisplatin,[4] folic acid,[5] and mercuric chloride,[6] and genetically determined progressive failure in mouse models of Alport's syndrome (reviewed by Poulsom *et al.*[7]) have been reported, and hypotheses have been generated to explain how cells from outside the kidney might modulate regenerative processes via transdifferentiation, cell fusion, or cytokine release.

Herrera and colleagues[8] (this issue) present a compelling case that interactions between CD44 and hyaluronans (hyaluronic acid (HA)) influence the way exogenous MSCs localize to kidneys with acute renal failure. These cells had been isolated from long bones of wild-type or CD44-null mice, and evidence of their MSC credentials included demonstration of their ability to show osteocyte or adipocyte phenotypes in specific culture conditions.

Using a range of sensitive morphological methods (Y-chromosome fluorescence *in situ* hybridization, preloading with iron-dextran nanoparticles, and fluorescent dye modification) to assess the origin of nuclei and other cellular elements, Herrera *et al.*[8] revealed that cells administered intravenously are soon found in peritubular capillaries, in the interstitial space, and even within damaged renal tubules, and this was accompanied by improvement in histological appearance and renal function as assessed by blood urea nitrogen levels.

So what's new? The fresh insight provided by Herrera and colleagues[8] derives from their evidence that the expression of CD44 on exogenous cells is important in helping the MSCs to localize to the damaged renal tissue *in vivo*. Wild-type MSCs with CD44 blocked by a neutralizing antibody were, as CD44-null cells, poor at reaching the damaged kidneys and did not improve blood urea nitrogen. Furthermore, the authors' studies *in vitro* supported the involvement of CD44 in chemotaxis toward purified HA, as CD44-null cells or null cells transfected to express a defective variant of CD44 did not migrate.

Another important point is that Herrera and colleagues' results[8] were obtained in a 'cell therapy' protocol rather than in a protocol that uses irradiation to pre-engraft cells throughout the recipient mouse. Irradiation is often used as a way to empty niches but might also encourage cell fusion. Whether cell fusion plays a part in the present results remains to be seen.

Precisely how deletion of CD44 impairs the localization of exogenous MSCs (or whether endogenous MSCs behave in the same way) has yet to be established, and it will be interesting to see how effective the MSCs generated here are for therapy of acute renal failure in CD44-null mice, which respond differently to damage. Nevertheless, expression by MSCs of CD44 as an integral receptor for HA is certainly involved, on the basis of the demonstration that truncated CD44 is ineffective at the binding of HA *in vitro* or at cell localization *in vivo*.

CD44 transcripts are subject to alternative splicing that contributes to the generation of a large family of protein isoforms and affects cell adhesion, but on the basis of the results here, a very basic cell mobility mechanism seems involved: CD44-null macrophages also have difficulty in migrating *in vivo* and attaching to vascular endothelium,[9] and the rapid constitutive motility of certain invasive breast cancer cell lines is reported to require interaction of HA with cells, activation of ERK1/2, and the participation of both cell-surface CD44 and another HA receptor, Rhamm (CD168).[10] So, it is possible that the CD44-null MSCs are disadvantaged in multiple ways — less able to move and less able to bind HA and matrix proteins.

One puzzling aspect of CD44-mediated 'targeting' of damaged kidneys is that the injected MSCs were said not to localize to the renal medulla despite the constitutive presence there of most of the renal HA (Figure 1). Considering that HA is found in many organs,

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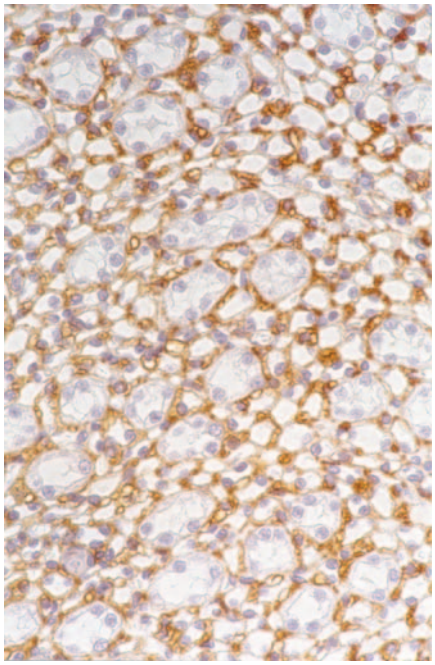

**Figure 1 |** Hyaluronan content in the kidney in a state of body hydration. (Reprinted from ref. 12.)

it will be interesting to learn whether CD44-dependent signals can influence the localization of cells to other damaged tissues and why the migrating MSCs do not get trapped in other HA-rich neighborhoods *en route*. It is known that complexity exists in the HA family of molecules and the proteins that attach to it — and that renal disease alters the structure and composition of the HA matrix, which in turn influences cell mobility (see, for example, Selbi *et al.*[11]). Perhaps particular molecular forms of HA generated by damage are better chemotactic agents, or synergy between various 'damage signals' makes the localization process dependent on CD44–HA interaction, but not directed by it?

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# Renal transplantation for ethnic minorities in Canada: Inequity in access and outcomes?

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**Among Canadians starting dialysis, patients of East Asian and Indo Asian background are less likely than whites to receive a renal allograft. Although the reasons for such variation are complex, less living donation may contribute significantly. More studies are needed to confirm these differences and to evaluate strategies for improving live kidney donation rates in communities at risk for low transplantation rates.**

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### Universal health and immigration: The Canadian identity

Universal health care is a pillar of Canada's national pride. The first public hospital insurance plan was created in the province of Saskatchewan in 1947, and this was eventually followed by a series of federal government acts culminating in the Canada Health Act of 1984. Principles of health-care delivery in Canada include public administration, comprehensiveness, universality, portability, and accessibility. All legal residents, including Canadian citizens and landed immigrants, are eligible to receive defined health-care benefits under this system, largely sustained by governmental revenue.

Another fundamentally defining Canadian characteristic is the encouragement of immigration. Canada's economic success attracts and is also sustained by immigration from far and wide. Canada has the highest percentage population growth rate from immigration among the G8 nations. There is large representation from East Asia and Indo Asia, regions that together contribute about one-half of the world's human population. Is it possible that in a country with an enviable health-care system, ethnicity can influence rates of kidney transplantation and its consequent success?

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